The Importance of Population Fertility and Consanguinity Data being available in Medico-Social Studies

Some data on consanguineous marriages in Northern Ireland

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IN recent years increasing use has been made of studies in the community as a means to better understanding of ætiology. At first the techniques used were essentially those developed in work on the epidemiology of infectious disease, but there have been developed more specific methods designed to illuminate the patterns of "constitutional" or degenerative disorders. The interpretation of the findings in work of this kind is often severely limited by the lack of adequate background data relating to the community from which the sample studied was drawn. Such considerations apply with peculiar force to studies in human variation where hereditary factors are of importance, because knowledge of the static and dynamic aspects of the mating and reproduction behaviour of the population is essential to an understanding of the pattern of such conditions. There is no doubt that the need for such studies is increasing and that they will constitute an essential part of balanced medical research activities in the future.

As the mean age of populations increases a higher proportion of disabling conditions than ever before is caused by the disorders present at birth, and by those determined by premature degeneration of tissues and organ systems which is the result, in considerable part, of inherited constitution. Further, appreciation of the size and nature of the potential problems in populations (and in specific populations) exposed in part or whole to radiation is handicapped at present by a lack of factual data relating to human populations. Finally, however carefully such an appreciation may be made, even with more knowledge of the population genetics of man, there will remain the necessity to observe by precise methods what changes in fact take place in exposed populations. Unless much preliminary knowledge is accumulated, the period of uncertainty about the effects of radiation from warlike or peaceful use of atomic energy may be unnecessarily prolonged. The data from population census figures and from the registration of births, deaths, and marriages is published in the United Kingdom by the Registrars General for England and Wales, Scotland and Northern Ireland.

From census data in the whole of the United Kingdom, reasonably accurate distributions in each county and in administrative areas are available every ten

years in respect of age, sex, marital condition, religion, occupation, and social class. From the registration procedures in all the countries information is available each year concerning births, marriages, and deaths during the year. Basic tabulations give (1) live births by sex and legitimacy, (2) marriages by age of partners, (3) deaths by age and certified cause.

In England and Wales and in Scotland stillbirths are also registered and the data published. Even more important in the present context, these countries also record and publish (as a result of the Population (Statistics) Act of 1938) much detailed information on fertility. This information about stillbirths and fertility is not available in Northern Ireland.

The purpose of the Population (Statistics) Act of 1938 was primarily to give data which would facilitate study of the trends of the age and sex compositions of the population, but it has had much additional value in illuminating the biological effects of age on fertility and in helping to understand the genetics of communities. In none of these countries do the Registrars General collect information on inbreeding in the population, or in other words, of the numbers of marriages where the partners are related in varying known degree.

It appears to us that such additional information on stillbirths, fertility, and inbreeding should be collected and made available in Northern Ireland for the reasons which we set out below. It seems to us that, from some points of view, it is even more important that the information should be available for Northern Ireland than for the rest of the United Kingdom. This is because it is possible, with a population of the size of Northern Ireland, to carry out studies in population genetics and human variation, which could only be done by an immense and largely impersonal organization in the rest of the United Kingdom. It may be noted that there are good precedents for innovations by Registrars General in Ireland, particularly in respect of census information. The remarkable collection published in each census from 1851 to 1911 of data relating to the deaf, blind, mentally affected, and physically handicapped is unique, and if similar information had been available for the United Kingdom in 1945 it would have simplified and improved much social planning.

The Value of Fertility Data and the Kind of Information Needed.

One of the fundamental conceptions in the modern theories of evolution is that differential fertility of persons of particular genetic types ultimately determine, at any given time, the genetic constitution of populations. Thus mutations which are unfavourable to survival are prevented from increasing in the population or fall in numbers to a low level at which they are part maintained by new mutations. Most expressions of new mutations in man take the form of what are biologically defects or deformities, or of a characteristic so bizarre that the possessor is, as a result, looked at askance in society. Whether the mechanism be biological or social, such individuals as a group tend to reproduce themselves less frequently than "normal" individuals. There are many examples from direct observation of such phenomena in populations. For example, boys with sex-linked progressive Duchenne type muscular dystrophy all die before reaching adult life and have a

zero fertility (Stevenson, 1953). Even in a condition such as hereditary deaf mutism, the fertility of affected subjects in Northern Ireland is probably only about one-third of that prevailing in the population as a whole (Stevenson and Cheeseman, 1956). The reverse situation, whereby favourable genes determine greater fertility in the group of those possessing them than that prevailing in the population as a whole, is less frequently observed; indeed, it seems likely that genes of positive evolutionary value seldom have a definite individual expression such that they may readily be recognised. In view of the socio-psychological pressures which tend to determine that people who are markedly "different" are not liked, this is understandable.

An example has recently been recognised which is of very great interest where there is good evidence that persons heterozygous for a particular gene have a better chance of survival in certain circumstances than the general population, although the homozygous expression of the gene is very unfavourable. Allison (1954 (a)) has shown that of the children with the sickle cell trait in endemic areas of subtertial malaria in tropical Africa a much smaller proportion than those with no sickling trait have the malarial parasites in their blood. Further injection of malarial parasites into adults who had not primarily been affected showed that those with sickle cell trait showed a very marked resistance to infection. It has been known for some time that those with sickling trait only were heterozygous for a recessive gene and that those who showed hæmolytic crises and sickle cell anæmia were homozygous for this gene. In large populations it would be expected that there would be a relationship between the frequency of the heterozygote and the homozygote and further, that as the condition is genetically determined the frequency of the two genotypes would vary little between separate populations. It has been demonstrated (Allison, 1954 (b)) that there are great variations in different areas and that these are related to the incidence of malaria. It is estimated that the proportion of descendants who reach maturity of the offspring of those heterozygous for a sickling gene is one and a quarter times that of the general population.

Recent observations that an undue proportion of persons who suffer from cancer of the stomach have a particular genotype determining a particular blood group (Aird, Bentall and Fraser Roberts, 1953) are also relevant to these considerations. A further example is the work of Struthers (1951) which suggests that an undue proportion of children with chronic bronchitis and asthma are of blood group A. Indeed it is generally agreed that no gene is entirely neutral in evolutionary value.

It is important to be able to estimate the rate at which known genes are lost to a population by the mechanism of diminished relative fertility. Estimates of this kind are essential to any indirect calculations of mutation rates in man, and as a majority of harmful genes are recessive, only indirect methods are available for human studies. In essence, such methods equate the number of genes lost to the number of new mutations needed to replace them and maintain a stable incidence of expression of the trait. Further, in any situation where an excess number of harmful genes arise in a population, an effect which could follow exposures to

radiation, the rate at which these genes would be eliminated is of fundamental importance. To estimate the speed of elimination, the fertility of the specific genotypes and that of the general population must be directly comparable and the information about each must therefore be available in the same form.

There are a few points about the assembly and interpretation of fertility data which are of particular importance in this important matter of determing the relative fertility of specific genotypes. In collecting information in a specific investigation the individuals whose fertility is of importance will be of varying ages and, if married, of different durations of marriage. In short, the information which can be collected will be (1) the numbers married and not married in each sex at each age, (2) the duration of marriage, (3) the number, condition, and ages of offspring of those married.

The information at present available in Northern Ireland concerning the whole population is not sufficient for direct comparison. Information comparable to (1) is available at each census, but there are no comparable data to (2) and (3). The information published by the Registrars General of England and Scotland coming from the data collected under the Population (Statistics) Act, 1938, is much more complete and parallels most of the information which can be collected in studies. There is no need to elaborate the range of this information, as the matter is fully considered in the Registrar General's Statistical Review for England and Wales for the years 1938 and 1939 (Text).

Consanguinity.

Consanguinity is of importance mainly in respect of the recessive gene determined conditions which constitute almost all the grave single gene expressions in man. Genes are said to be recessive when there is expression of the trait or characteristic determined by the gene in the homozygote but not in the heterozygote. The heterozygote, having only one "abnormal" gene, will have received it from only one parent while the homozygote having the two abnormal genes must have received one from each parent.

The frequency of persons homozygous for any unfavourable gene in man is always low and an undue proportion of affected subjects have parents who have had, within a few generations, a common ancestor. The explanation is, of course, that if a given person is heterozygous for a given gene any of his relatives descended from a common ancestor whom he marries is much more likely to be heterozygous for the same gene than a mate chosen at random in the general population.

Suppose, for example, that in a rare condition one in a thousand of the population was heterozygous for a particular gene. If a given man who was heterozygous for that gene married at random in the population the chance of his marrying another heterozygote would be one in a thousand. If, however, he married any full cousin, as he and his cousin must have had one pair of common grandparents, the chance of his cousin being heterozygous for the gene would only be $\frac{1}{8}$. (The probability of a gene being derived from the parent through whom the cousin relationship occurs is $\frac{1}{2}$ (either father or mother). The chance of the sib of the heterozygote parent (the uncle or aunt) having the gene is $\frac{1}{2}$. The chance of each of his or her

offspring (the cousin who may be married) having the gene is $\frac{1}{2}$. The chance of any given cousin being heterozygous is therefore $\frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} = \frac{1}{8}$.)

A little consideration of the above will make clear the four following propositions :

1. *That the less common the gene the higher will be the proportion of affected subjects having related parents.*

Logically, if a completely new mutation occurs for the first time in the population, it would never occur in the homozygous state and therefore be manifest until there occurred a marriage of persons descended from a common ancestor.

2. *That there should be a numerical relationship between the frequency of the recessive gene and the proportion of homozygotes who have related parents in a given degree, e.g., full cousins.*

This numerical relationship will, however, be varied by the number of consanguineous marriages which take place in the population. There will be three "bands of frequencies" of cousin marriages in a community. In the first no such marriage will occur—for example, in a strict Roman Catholic community. In the second, cousin marriages would occur no more frequently than by mere chance, so that if a man had x female cousins his chance of marrying one would be no more frequent than x multiplied by the inverse of the number of potential spouses in the whole community. Such a situation would make cousin marriages very uncommon. The third, which is in practice what is always observed, is a frequency of cousin marriages which probably varies considerably in different communities, but it is in all considerably greater than would occur by mere chance. This is because of physical isolation of small communities, because opportunities for meeting spouses are not unlimited, and because religious and economic cleavages limit choice. Various social pressures, some, for example, connected with land holding and inheritance customs in rural communities, may also limit choice of a partner. It follows that, in relating the frequency of a gene to a cousin marriage rate, the prevailing cousin marriage rate in the community concerned must be taken into account.

The numerical relationship between the frequency of the recessive gene determining the trait, the proportion of affected homozygotes who have full-cousin parents, and the prevailing full-cousin marriage rate in the community concerned is conveniently expressed in a formula derived by Lenz (1919). Dahlberg (1929) has subsequently produced a more sophisticated version, but the principle is more easily explained by considering Lenz's original formula, which is

$$F = \alpha / (\alpha + 16q)$$

where F is the proportion of cousin marriages in all marriages which would be expected to give rise to homozygous affected offsprings, α is the chance of an individual in the community marrying a first cousin, and q is the gene frequency of the abnormal gene. (For those interested, the derivation of this formula is adequately explained in Penrose (1948)).

It will be apparent, therefore, that F can be estimated by knowing the frequency of the condition and the prevailing cousin marriage rate. A value can also be

obtained by direct observation of the proportion of the parents (matings) of affected persons who prove to be full cousins.

Comparison of the two values for F will enable confirmation or otherwise that the condition being studied is probably determined by a single gene fully recessive. It will also be clear that the value of $\propto$ is critical in determining the estimated value of F, and that for the formula to be of value, cousin marriage rates must be accurately determined.

3. *That the relationship in 2 above is also a test of the specifity of one gene to the condition.*

There are a number of conditions where the characteristic or trait may be the expression in the homozygote in some instances of one recessive gene and in others of entirely different recessive genes. If it is impossible clinically to differentiate these homozygous expressions it might never be suspected that more than one gene could be responsible for the condition. The situation would be suspected if, when two homozygotes married, sometimes all and sometimes none of their offspring showed the trait. However, marriage of homozygotes (except in recessive deaf mutism) is a phenomenon of extreme rarity. Yet, as has been noted, if the prevailing cousin marriage rate in a community is known, and the frequency of the homozygote is also known, then the expected proportion could be estimated of subjects showing the trait whose parents were full cousins. If, however, more than one homozygote genotype was causing the condition, then the frequency of the separate genes would each be lower than if only one gene was involved, and the observed frequency of full-cousin parents would exceed that expected in the single gene hypothesis. Such reasoning leads us to expect a parent cousin marriage rate, based on the frequency of albinism of about 6 per cent. The observed parent cousin marriage rate is, in fact, about 20 per cent. (Roberts, 1940).

An interesting observation of the same kind has recently been made in Northern Ireland, where the evidence from similar calculations that more than one gene can cause deaf mutism is reinforced by study of the marriages of hereditary deaf mutes which sometimes results in deaf and sometimes hearing offspring. The cousin marriage rate in Northern Ireland from the inadequate data available is estimated as 1 per cent. The incidence of deaf mutism is 0.00023. The expected frequency of full-cousin parent marriages on a single gene hypothesis would be 4.23 per cent. The observed frequency was 9.5 per cent.

It is not unlikely that other supposed single recessive gene determined conditions are really heterogeneous in genetical origin, and it is important to have as accurate knowledge as possible about the distribution in the population of recessive genes in man. Such information is essential both in calculation of the possible effects of harmful radiations and in the recognition of their effects. Failure to appreciate that more than one recessive gene could determine the same inherited traits could be very misleading. PUBLISHED DATA ON CONSANGUINITY.

We cannot trace any published figures relating to consanguineous marriage rates in Ireland and, as is well known, only Bell (1940) has recorded any considerable body of data for England and Wales.

It is likely that the whole trend in countries which have undergone social revolutions with accompanying industrialization, and improvements in communication is for the frequency of marriages of those related in ascertainable degrees to fall. The effect of breakdown of isolated communities so determined will be to make more homogeneous the consanguineous marriage rates in different districts in given countries. Nevertheless, such differences persist and are of importance.

Table 1 illustrates that the range of variation between and within countries is large enough to invalidate the kinds of calculation mentioned previously in this paper.

TABLE 1.

ESTIMATES OF THE FREQUENCY OF COUSIN MARRIAGES IN VARIOUS POPULATIONS MADE IN THE LAST 25 YEARS.

Reporters	Population	Years of Study	Number of Marriages	Cousin Marriages per cent.
Dahlberg, 1929 ...	Bavaria ...	1926-1933 ...	...	0.20
	40 Parishes, rural Bavaria...	1925 ...	16182 ...	0.6
	1 Community, Switzerland...	1931 ...	270 ...	1.9
	1 Community, Obermatt, Switzerland ...	1934 ...	52 ...	11.5
	Sample, Island Bornholm, Denmark ...	1938 ...	399 ...	1.3
Böök, 1948 ...	Sample, Copenhagen, Denmark ...	1941 ...	498 ...	1.2
	1 Rural District, Northern Sweden ...	1948 ...	843 ...	0.9
	I Rural District, Northern Sweden ...	1948 ...	281 ...	2.8
	1 Rural District, Northern Sweden ...	1948 ...	191 ...	6.8
Neel, Kodani, Brewer, and Anderson, 1949 ...	Hiroshima, Kure, and Nagasaki ...	1949 ...	24000 ...	4 (approx.)
Bell, 1940 ...	Parents of 10,236 children in general hospitals	1925-1939 ...	10236 ...	0.4

Additional information on consanguineous marriage rates in different countries have been published by other authors. However, in these countries the complete data showing the size of the population and mode of the selection of the sample are not given and/or the proportion of the consanguineous marriages where the parents were full cousins is not stated. (Bartels (1941), quoted by Lindenov (1945), referring to the Netherlands.)

It will be seen that there is a great dearth of good recent data and that such as is available is heterogenous, in that it deals with marriages which occurred at different periods of varying length in different countries. What is needed is continuously recorded data, from different countries, in each case the sample being of such size and nature that isolate effects can be detected, and trends observed. Further, in every instance, the precise consanguineous relationships of the partners to the marriages should be stated.

The Northern Ireland Data.

Table 2 sets out some data which have been collected in recent years in Northern Ireland.

TABLE 2.

The Available Information on Consanguinity in Northern Ireland.

	No. of Marriages	C_1	C_2	C_3	C_χ	% C_1	% All C
County Fermanagh, 1954	350	1	1	4	–	0.28	1.71
County Londonderry, 1954	717	10	–	12	1	1.39	3.3
County Tyrone, 1954	3000	6*	4	4	–	0.20	0.47
County Armagh, 1954	560	3	1	3	–	0.54	1.25
City of Londonderry, 1955	162	–	–	–	–	–	–
Registrar General's Return of Marriages, 1954-55	5333	7	–	28	–	0.13	0.66
Mathers, 1952	670	1	1	–	–	0.15	0.30
Medical Students (Q.U.B., 1953-54)	116	–	–	1	1	–	1.72

*One of these was closer than first-cousin relationship. This is included in preceding figure.

Note. C_1, C_2, and C_3 refer to matings of first cousins, first cousins once removed and second cousins respectively, as defined in the Oxford Dictionary. C_χ refers to degrees of relationship less close than above but where the partners had a common ancestor.

The information referred to the counties was collected in 1954 by the health visitors when paying visits to the homes where there were new-born children. It may be assumed that the great majority of the marriages took place in the preceding ten years.

The medical student's data refer to two classes where the students were invited to complete a card detailing any known relationship between their parents. One of us (J. D. M.) assembled his data by questioning 670 successive married persons coming to the Casualty Department of the Royal Victoria Hospital, Belfast, with minor injuries and superficial sepsis.

The Registrar General's data were collected by the co-operation of about half of the Protestant clergy and ministers, over the year 1954, when questioning persons about to be married to ensure that they were not within illegal degrees of relationship. The information relates to areas scattered fairly uniformly over

the Six Counties. It seems likely to be the most intrinsically reliable of the sources and it also relates to the most recent marriages which is of particular interest.

It is unlikely, in view of the independent evidence from these scattered sources, that the full-cousin marriage rate in recent years is as much as 1 per cent. It may, however, have been higher in the past, and this has to be taken into account on appropriate occasions.

As will be seen from Table 3, which is derived from the data in the four counties, the proportion of full-cousin marriages is significantly less in Roman Catholics. This low proportion has presumably prevailed for a long time so that the decline in rate which is probably occurring is entirely in the Protestant population. It is noticeable, however, that there is a greater proportion of first cousin once removed (C_3) marriages in Roman Catholics. It is difficult to interpret this observation.

TABLE 3.

CONSANGUINEOUS MARRIAGES IN PARENTS OF NEW-BORN CHILDREN IN COUNTIES ARMAGH, FERMANAGH, LONDONDERRY, AND TYRONE, 1954.

RELIGION	Consanguineous Marriages in each Degree of Relationship and Percentage in each Case of Total Marriage									
	C_1		C_2		C_3		Cx		TOTAL	
	No.	%	No.	%	No.	%	No.	%	No.	%
Protestant - - -	12	1.60	2	0.27	6	0.80	1	0.13	21	2.80
Roman Catholic - -	2	0.23	–	–	13	1.51	–	–	15	1.74
TOTAL - -	14	0.87	2	0.12	19	1.18	1	0.06	36	2.23

It is clear that better data are required and that only constant careful collection will disclose trends and ensure accuracy when relating incidence of recessive gene determined conditions in young children to consanguinity rates.

SUMMARY.

This paper presents arguments in favour of accumulation of data on fertility and "inbreeding" in the population of Northern Ireland. The reasons advanced are that such data are essential as a background to population genetic studies. It is suggested that such studies are of increasing importance in two ways. Firstly, the understanding of many chronic disabling disorders, and, secondly, in providing some of the information, at present scanty or missing, which is necessary for an understanding of the extent of the problem of exposure of populations to radiations. It is pointed out that the data available from the Population Statistics Act (1938) and the recording of consanguineous marriages would meet all needs at present.

Some data on prevailing consanguineous marriage rates in Northern Ireland are recorded.

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